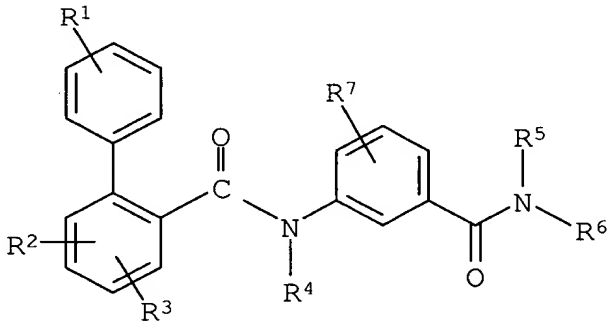
BIPHENYLCARBOXYLIC ACID AMIDES, THE PREPARATION THEREOF AND THE USE THEREOF AS MEDICAMENTS

Related Applications

Benefit of U.S. Provisional Application Serial No. 60/220,115, filed on July 24, 2000, is hereby claimed and said application is hereby incorporated by reference in its entirety.

Field of the Invention

The present invention relates to biphenylcarboxylic acid amides of general formula



, (I)

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof which have valuable pharmacological properties, medicaments containing these compounds, their use and processes for preparing them.

The compounds of the above general formula I are valuable inhibitors of the microsomal triglyceride transfer protein (MTP) and are therefore suitable for lowering the plasma level of the atherogenic lipoproteins.

In the above general formula I

R^1, R^2 and R^3, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom, a straight-chain or branched C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino- or di-(C_{1-3}-alkyl)-amino group,

wherein R^1 and R^2 in the ortho,ortho' position of the biphenyl group of formula I together may also denote a carbonyl group,

R^4 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^5 denotes a hydrogen atom or a straight-chain or branched C_{1-6}-alkyl group and

R^6 denotes a straight-chain or branched C_{1-6}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

an arylamino, N-(C_{1-3}-alkyl)-arylamino, heteroarylamino, N-(C_{1-3}-alkyl)-heteroarylamino, C_{1-7}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-7}-alkyl-carbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-heteroarylcarbonylamino, C_{1-8}-alkoxy-carbonyl-amino or N-(C_{1-3}-alkyl)-(C_{1-8}-alkoxy)-carbonylamino group,

an aryl, aryl-carbonyl-aryl, aryl-C_{1-3}-alkoxy-aryl or aryl-C_{1-3}-alkyl-aryl group,

a heteroaryl group,

an aryl group substituted by a heteroaryl group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-aryl group, while

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group, or

the two hydrogen atoms of the methylene group in the 3 position of a cyclopentyl group or in the 3- or 4-position of a cyclohexyl or cycloheptyl group may be replaced by an n-butylene, n-pentylene, n-hexylene, 1,2-ethylenedioxy or 1,3-propylenedioxy group or

in a 5- or 6-membered cycloalkyl group one or two single bonds separated from each other and from position 1 by at least one bond may each be fused with a phenyl group,

a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group,

a straight-chain C_{1-4}-alkyl group optionally substituted in the 1 position by a C_{3-5}-cycloalkyl group or a C_{1-3}-alkyl group, which is terminally substituted

by an aryl or heteroaryl group,

by an aryl-C C-, heteroaryl-C C-, aryl-CH=CH- or heteroaryl-CH=CH- group,

by an aryl group which is fused to a heteroaryl group via two adjacent carbon atoms,

by a heteroaryl group which is fused to an aryl or heteroaryl group via two adjacent carbon atoms or, in the case of a 5-membered heteroaryl group, via an imino nitrogen atom and an adjacent carbon atom,

by an aryl group which is substituted

by an aryl or heteroaryl group,

by a C_{3-7}-cycloalkyl group or a 4 to 7 membered cycloalkyleneimino group, which

may each be fused to a phenyl ring via two adjacent carbon atoms or

wherein the two hydrogen atoms of the methylene group in the 3 position of a 5-membered ring or in position 3 or 4 of a 6- or 7-membered ring may be replaced by an n-butylene, n-pentylene, n-hexylene, 1,2-ethylenedioxy or 1,3-propylenedioxy group or by an oxygen atom or

wherein in each case the methylene group in the 4 position of a 6- or 7-membered ring may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-8}-alkyl-carbonyl, C_{1-8}-alkoxycarbonyl, benzoyl, phenyl-(C_{1-3}-alkyl-carbonyl), C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

or by a phenylaminosulphonyl or phenylsulphonylamino group,

by a C_{3-7}-cycloalkyl group wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted

by a C_{1-3}-alkyl, phenyl, C_{1-8}-alkyl-carbonyl, C_{1-8}-alkoxycarbonyl, benzoyl, phenyl-(C_{1-3}-alkylcarbonyl), C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group,

by a heteroarylcarbonylamino-aryl, heteroarylaminocarbonyl-aryl, heteroarylcarbonyl-N-(C_{1-3}-alkyl)-amino-aryl or heteroaryl-N-(C_{1-3}-alkyl)-aminocarbonyl-aryl group,

by a straight-chain or branched C_{4-7}-alkyl-carbonylamino-aryl or N-(C_{1-3}-alkyl)-C_{4-7}-alkyl-carbonylamino-aryl group,

by a C_{3-7}-cycloalkyl-carbonylamino-aryl or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-carbonylamino-aryl group,

by a C_{3-7}-Cycloalkyl-aminocarbonyl-aryl or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-aminocarbonyl-aryl group,

by a cycloalkyleneimino-carbonylamino-aryl or cycloalkyleneimino-carbonyl-N-(C_{1-3}-alkyl)-amino-aryl group wherein the cycloalkyleneimino moiety is 4- to 7-membered,

by an aryl-aminocarbonylamino-aryl group wherein one or both amino-hydrogen atoms may each be replaced by a C_{1-3}-alkyl group,

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, C_{3-7}-cyclo-alkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aryl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group or

by an aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, aryl-C_{1-3}-alkyl-aminocarbonyl, N-(C_{1-3}-alkyl)-aryl-C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl-aminocarbonyl or C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl-aminocarbonyl group,

a straight-chain or branched C_{2-6}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, aryloxy, heteroaryloxy- aryl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino or N-(C_{1-3}-alkyl)-heteroarylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a 4- to 7-membered cycloalkyleneimino group wherein the cycloalkylene moiety may be fused to a phenyl ring,

R^7 denotes a hydrogen, fluorine, chlorine, bromine or iodine atom, a C_{1-3}-alkyl, C_{1-3}-alkoxy, nitro or amino group,

wherein by the term aryl group mentioned above is meant a phenyl, 1-naphthyl or 2-naphthyl group,

by the term heteroaryl group mentioned above is meant a 5-membered heteroaromatic ring linked via a nitrogen or carbon atom, which contains

an imino group, an oxygen or sulphur atom,

an imino group and an oxygen, sulphur or nitrogen atom,

an imino group and two nitrogen atoms or

an oxygen or sulphur atom and two nitrogen atoms,

or a 6-membered heteroaromatic ring linked via a carbon atom which contains one or two nitrogen atoms,

and wherein a 1,4-butadienylene group may be attached both to the abovementioned 5-membered heteroaromatic rings via two adjacent carbon atoms or via an imino nitrogen atom and an adjacent carbon atom and also to the 6-membered heteroaromatic rings in each case via two adjacent carbon atoms and the bicyclic heteroaromatic rings thus formed may also be bonded via a carbon atom of the 1,4- butadienylene group,

a hydrogen atom bonded to a nitrogen atom of the abovementioned 5-membered monocyclic or fused heteroaryl groups may be replaced by a C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl, phenylcarbonyl or phenyl-C_{1-3}-alkylcarbonyl group,

all the abovementioned phenyl, aryl and heteroaryl groups as well as aromatic or heteroaromatic parts of molecules in the carbon skeleton may be monosubstituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl or a 4- to 7-membered cycloalkyleneimino group, while

in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be replaced by an oxygen or sulphur atom, by a sulphinyl or sulphonyl group or by an imino group optionally substituted by a C_{1-5}-alkyl, phenyl, C_{1-4}-alkyl-carbonyl, C_{1-4}-alkoxy-carbonyl, C_{1-3}-alkyl-aminocarbonyl or di-(C_{1-3}-alkyl)-aminocarbonyl group,

by a trifluoromethyl, phenyl, hydroxy, C_{1-3}-alkoxy, phenyl-C_{1-3}-alkoxy, difluoromethoxy, trifluoromethoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, amino-C_{1-3}-alkyl, tert.butoxycarbonylamino-C_{1-3}-alkyl, C_{1-3}-alkylamino-C_{1-3}-alkyl,

di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl, amino-C_{1-3}-alkyl-carbonyl-amino, C_{1-3}-alkylamino-C_{1-3}-alkyl-carbonyl-amino, di-(C_{1-3}-alkyl)-amino-C_{1-3}-alkyl-carbonyl-amino, phenylamino, N-(C_{1-3}-alkyl)-phenylamino, acetylamino, propionylamino, benzoylamino, N-(C_{1-3}-alkyl)-benzoylamino, acetyl, propionyl, benzoyl, hydroxycarbonyl, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, 2,2,2-trifluoroethyl-aminocarbonyl or di-(C_{1-3}-alkyl)aminocarbonyl group, by a 4- to 7-membered cycloalkyleneimino-carbonyl group or a cyano group or, with the exception of 5-membered heteroaryl groups or heteroaromatic parts of molecules containing more than two heteroatoms, may also be disubstituted by one of the abovementioned substituents and one substituent selected from among fluorine, chlorine, bromine, C_{1-3}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, hydroxy and amino, wherein two adjacent hydrogen atoms in a phenyl group or a phenyl moiety contained in the groups defined above may also be replaced by a methylenedioxy or 1,2-ethylenedioxy group, or may also be trisubstituted by three substituents selected from among fluorine, chlorine and bromine atoms and C_{1-3}-alkyl groups, wherein the substituents may be identical or different and the abovementioned phenyl groups or phenyl moieties may in turn be substituted by a fluorine, chlorine or bromine atom, by a methyl, trifluoromethyl or methoxy group,

in all the abovementioned 4- to 7-membered cycloalkyleneimino groups the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms in each case may be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxycarbonyl, C_{1-6}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl or sulphonyl group or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl,

phenyl-C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

the hydrogen atoms in the C_{1-3}-alkyl and alkoxy groups mentioned in the definition of the above groups may be wholly or partially replaced by fluorine atoms,

additionally any carboxy, amino or imino group present in the abovementioned groups may be substituted by a group which can be cleaved *in vivo*, and may thus occur in the form of a prodrug group,

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxy-carbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl- C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO-O-(R_fCR_g)-O group wherein R_e to R_g are as hereinbefore defined,

whereby the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group.

Moreover, the saturated alkyl and alkoxy moieties which contain more than 2 carbon atoms mentioned hereinbefore and hereinafter in the definitions also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc., unless otherwise stated.

Preferred compounds of the above general formula I are those wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms,

R^2 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R^1 and R^2 in the ortho, ortho' position of the biphenyl group of formula I together denote a carbonyl group,

R^3, R^4 and R^5 which may be identical or different, each denote a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, C_{1-8}-alkoxy-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-aminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylamino, 1-naphthylamino or 2-naphthylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group,

a C_{1-4}-alkyl-carbonylamino, phenylcarbonylamino or C_{1-8}-alkoxy-carbonylamino group,

a phenyl, biphenyl, 1-naphthyl, 2-naphthyl, phenylcarbonyl-phenyl, phenyl-C_{1-3}-alkoxyphenyl or phenyl-C_{1-3}-alkylphenyl group which may be substituted in the aromatic moieties in each case by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, benzoylamino, acetyl, benzoyl, C_{1-3}-alkylamino-carbonyl or cyano group,

a heteroaryl group or a heteroaryl-phenyl group,

a C_{3-7}-cycloalkyl or C_{3-7}-cycloalkyl-phenyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group, or

the two hydrogen atoms of the methylene group in the 3 position of a cyclopentyl group or in the 4-position of a cyclohexyl group may be replaced by an n-butylene, n-pentylene, 1,2-ethylenedioxy or 1,3-propylenedioxy group or

in a cyclopentyl or cyclohexyl group one or two single bonds separated from each other and from position 1 by at least one bond may each be fused to a phenyl group,

a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group,

a straight-chain C_{1-4}-alkyl group optionally substituted in the 1 position by a cyclopropyl group or a C_{1-3}-alkyl group, which is terminally substituted

by a phenyl, biphenyl, 1-naphthyl or 2-naphthyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, a straight-chain or branched C_{1-4}-alkyl group, a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, difluoromethoxy, benzyloxy, aminomethyl, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenylamino, N-(C_{1-3}-alkyl)-phenylamino, acetylamino, acetyl, propionyl, benzoyl, hydroxycarbonyl, C_{1-4}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)aminocarbonyl, 2,2,2-trifluoroethylaminocarbonyl, pyrrolidinocarbonyl, piperidinocarbonyl or cyano group wherein two adjacent hydrogen atoms may also be replaced by a methylenedioxy or 1,2-ethylenedioxy group,

by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl or C_{1-3}-alkoxy group, by a trifluoromethyl, phenyl or cyano group,

by a phenyl-C C- or phenyl-CH=CH- group which may be substituted in the phenyl moiety by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl or C_{1-3}-alkoxy group, by a trifluoromethyl, dimethylamino, phenyl or cyano group,

by an indolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl group bonded via a carbon atom or, in the case of the first two groups, via a nitrogen atom,

by a phenyl group which is substituted by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl, trifluoromethyl, phenyl or cyano group,

by a C_{5-6}-cycloalkyl group or a 5- or 6-membered cycloalkyleneimino group which

may be fused to a phenyl ring in each case via two adjacent carbon atoms or

wherein the two hydrogen atoms of the methylene group in the 3 position of a 5-membered ring or in the 4 position of a 6-membered ring may be replaced by an n-butylene, n-pentylene, n-hexylene, 1,2-ethylenedioxy or 1,3-propylenedioxy group or by an oxygen atom or

wherein the methylene group in the 4 position of a 6-membered ring may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-4}-alkyl-carbonyl, C_{1-4}-alkoxy-carbonyl or benzoyl group,

by a phenylaminosulphonylphenyl or phenylsulphonyl-aminophenyl group,

by a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group, phenyl-C_{1-3}-alkyl-aminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkyl-aminocarbonyl-phenyl,

C_{3-7}-cycloalkyl-carbonylamino-phenyl,
N-(C_{1-3}-alkyl)-C_{3-7}-aycloalkyl-carbonylamino-phenyl,
C_{3-7}-cycloalkyl-aminocarbonyl-phenyl,
N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-aminocarbonyl-phenyl, C_{4-6}-alkyl-carbonylamino-phenyl,
N-(C_{1-3}-alkyl)-C_{4-6}-alkyl-carbonylamino-phenyl, heteroarylcarbonylamino-phenyl,
N-(C_{1-3}-alkyl)-heteroarylcarbonylamino-phenyl, pyrrolidinocarbonyl-amino-phenyl,
piperidinocarbonyl-amino-phenyl, N-(C_{1-3}-alkyl)-pyrrolidinocarbonyl-amino-phenyl,
N-(C_{1-3}-alkyl)-piperidinocarbonyl-amino-phenyl, phenylaminocarbonylamino-phenyl,
N-(C_{1-3}-alkyl)-phenylaminocarbonylamino-phenyl or
N,N-di-(C_{1-3}-alkyl)-phenylaminocarbonylamino-phenyl group,

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, phenyloxycarbonyl or heteroaryloxycarbonyl group,

by an aminocarbonyl, C_{1-3}-alkyl-aminocarbonyl, benzyl-aminocarbonyl,
di-(C_{1-3}-alkyl)-aminocarbonyl, aminocarbonyl-C_{1-3}-alkyl-aminocarbonyl or
C_{1-3}-alkoxy-carbonyl-C_{1-3}-alkyl-aminocarbonyl group,

a straight-chain C_{2-3}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, phenoxy or phenyl-C_{1-3}-alkoxy group or

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino,
N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, phenylcarbonylamino or
N-(C_{1-3}-alkyl)phenylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a pyrrolidino or piperidino group which

may each be fused via two adjacent carbon atoms to a phenyl ring optionally substituted by one or two C_{1-3}-alkoxy groups, by an amino, C_{1-3}-alkylamino, acetylamino, aminomethylcarbonylamino or dimethylaminomethylcarbonylamino group,

or a piperazino, morpholino or thiomorpholino group, while the nitrogen atom in the 4 position of the piperazino group may be substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl or phenylaminocarbonyl group, and

R^7 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group or a nitro or amino group,

while, unless otherwise specified, by the term heteroaryl group mentioned above is meant a 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, [1,2,3]-thiadiazol-4-yl, benzimidazol-2-yl, benzimidazol-5-yl, or imidazo-[1,2-a]pyridin-2-yl group optionally substituted in the carbon skeleton by up to three C_{1-3}-alkyl groups and

all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules may optionally additionally be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, by a cyano group or by a straight-chain or branched C_{1-3}-alkyl or trifluoromethyl group,

and/or a hydrogen atom bonded to a nitrogen atom of a heteroaryl group or heteroaromatic part of a molecule may be replaced by a C_{1-3}-alkyl, phenyl or C_{1-3}-alkylcarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl or trifluoromethyl group,

R^2 denotes a hydrogen atom or a C_{1-3}-alkyl group or

R^1 and R^2 in the ortho, ortho' position of the biphenyl group of formula I may together also denote a carbonyl group,

R^3 and R^4 each denote a hydrogen atom,

R^5 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

a phenyl, biphenyl or phenyl-C_{1-3}-alkylphenyl group,

a straight-chain C_{1-3}-alkyl group optionally substituted in the 1 position by a cyclopropyl group or a C_{1-3}-alkyl group which is terminally substituted

by a phenyl or biphenyl group which may be substituted in each case by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl, hydroxy, phenylamino or N-(C_{1-3}-alkyl)-phenylamino group,

by a 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-benzimidazol-2-yl group,

by a phenyl group which is substituted by a 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, [1,2,3]-thiadiazol-4-yl, benzimidazol-2-yl

or imidazo-[1,2-a]pyridin-2-yl group, wherein the abovementioned heteroaromatic groups may be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, by a phenyl, C_{1-4}-alkyl, trifluoromethyl, C_{1-3}-alkoxy, dimethylamino or C_{3-7}-cycloalkyl group,

by a phenyl group which is substituted by a pyrrolidino or piperidino group optionally fused to a phenyl group,

by a phenyl-C C- group which may be substituted in the phenyl moiety by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-4}-alkyl or C_{1-3}-alkoxy group, by a trifluoromethyl or phenyl group,

by a 4-piperidinyl group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylamino-carbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group optionally substituted in the terminal phenyl moieties by a C_{1-3}-alkyl group

or

by a heteroaryl-carbonylamino-phenyl or N-(C_{1-3}-alkyl)-heteroaryl-carbonylamino-phenyl group, wherein the heteroaryl moiety is selected from among 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl and [1,2,3]-thiadiazol-4-yl, wherein a hydrogen atom bound to a nitrogen atom of a heteroaromatic group and/or a hydrogen atom bound to a carbon atom of a heteroaromatic group may in each case be replaced by a C_{1-3}-alkyl group, and

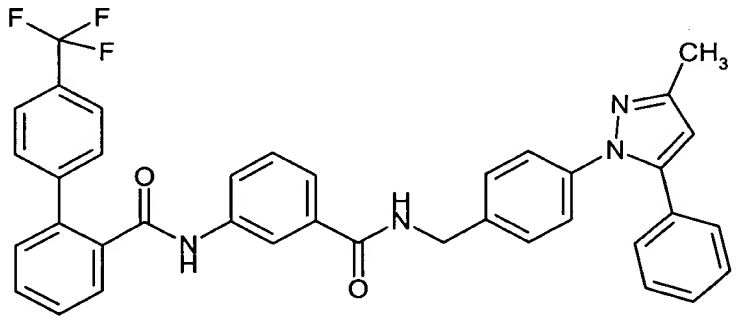
R^7 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group or an amino group,

while all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules in the carbon skeleton may optionally additionally be substituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-3}-alkyl group, by a cyano or a trifluoromethyl group,

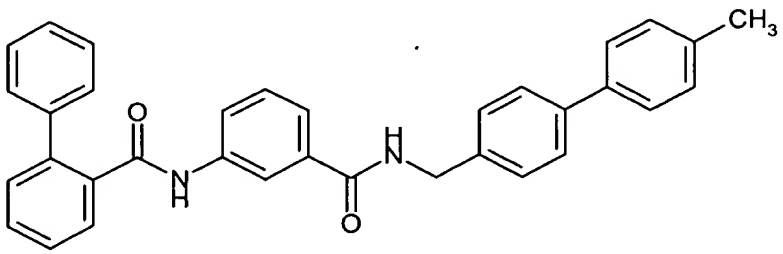
the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

The following are mentioned as examples of particularly preferred compounds:

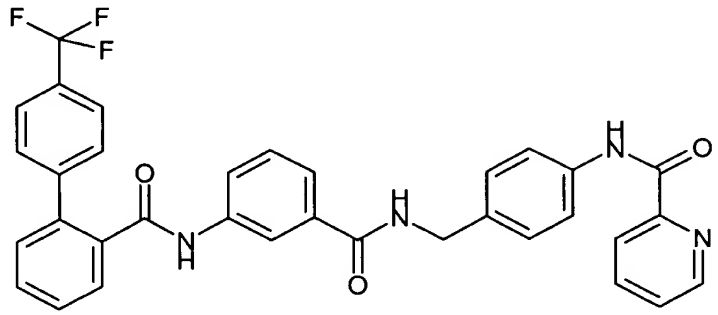
(a) N-[4-(3-Methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide



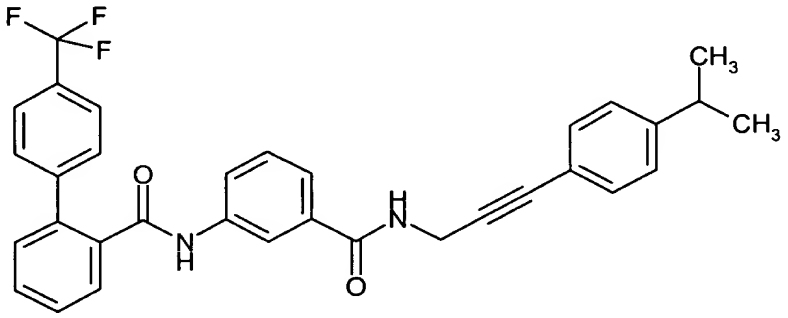
(b) N-(4'-Methylbiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)- benzoic acid amide



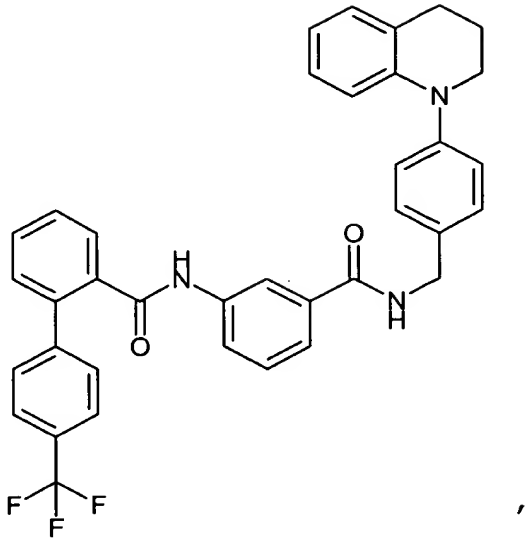
(c) N-[4-(Pyridin-2-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)- benzoic acid amide,



(d) N-[3-(4-Isopropylphenyl)-prop-2-in-yl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and



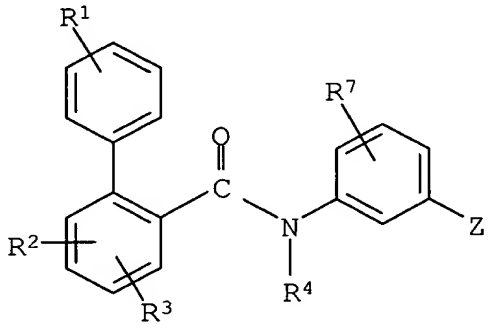
(e) N-[4-(1,2,3,4-Tetrahydrochinolin-1-yl)-phenylmethyl]-3-(4'-trifluormethylbiphenyl-2-carbonylamino)-benzoic acid amide



and the salts thereof.

According to the invention, the new compounds are obtained by methods known from the literature, e.g. by the following methods:

a. reacting a compound of general formula

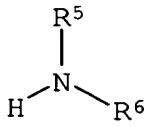


, (II)

wherein

R^1 to R^4 and R^7 are as hereinbefore defined, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

with an amine of general formula



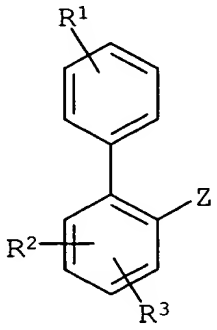
, (III)

wherein

R^5 and R^6 are as hereinbefore defined.

The reaction is expediently carried out with a corresponding halide or anhydride of general formula III in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or sulpholane optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C. However, it may also be carried out with the free acid, optionally in the presence of an acid-activating agent, e.g. propanephosphonic acid cycloanhydride or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate (TBTU), or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl carbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

b. reacting a compound of general formula

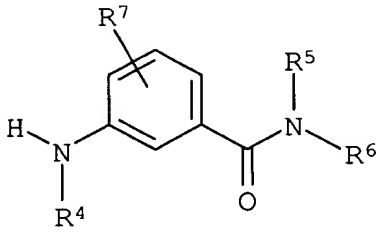


, (IV)

wherein

R^1 to R^3 are as hereinbefore defined, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

with an amine of general formula



, (V)

wherein

R^4 and R^7 are as hereinbefore defined.

The reaction may be carried out in accordance with the conditions mentioned above for method (a).

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I or

if a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I or

if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained which contains a carboxy or ester group, this may be converted by amidation into a corresponding amide of general formula I.

The subsequent acylation or sulphonylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding acyl or sulphonyl derivative, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride or sodium cyanoborohydride, expediently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. However, the methylation is preferably carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or most advantageously in a corresponding alcohol optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benztriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent amidation is carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine, optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, while the amine used may act as solvent at the same time, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate, N,N'-dicyclohexylcarbodiimide,

N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benztriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, tert.butyl-dimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxy-benzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C. However, a silyl group may also be cleaved using tetrabutylammonium fluoride as described hereinbefore.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane, optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon

atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

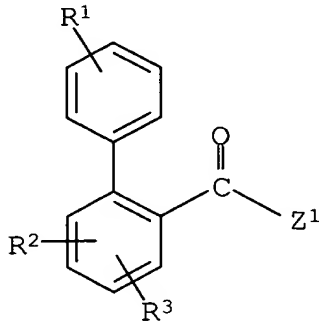
The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain an acidic group such as a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

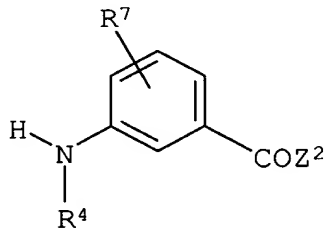
The compounds of general formulae II to V used as starting materials are either known from the literature or may be obtained by methods known from the literature or are described in the Examples.

A compound of general formula II is obtained, for example, by reacting a compound of general formula



, (VI)

wherein R^1 to R^3 are as hereinbefore defined and Z^1 denotes a carboxy group or a reactive derivative of a carboxy group, with an amine of general formula



, (VII)

wherein R^4 to R^7 are as hereinbefore defined and Z^2 denotes a protecting group for a carboxy group, and subsequently cleaving the protecting group.

The amines of general formula III wherein R^6 denotes a heteroaryl-aryl group or a heteroaryl-aryl-C_{1-6}-alkyl group, may be prepared, for example, by synthesising the heteroaromatic ring from suitably substituted aryl or aryl-C_{1-6}-alkyl educts, possibly by reactions of condensation with suitable dicarbonyl compounds.

The biphenyl-2-carboxylic acids according to general formula IV are known from the literature or may be prepared by methods known from the literature from corresponding biphenyl educts.

The 3-amino-benzoic acid amides according to general formula VI are also known from the literature or may easily be prepared from optionally substituted 3-aminobenzoic acids by reacting with the corresponding amines.

As already mentioned hereinbefore, the compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. In particular, they are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma levels of the atherogenic lipoproteins.

For example, the compounds according to the invention were investigated for their biological effects as follows:

Inhibitors of MTP were identified by a cell-free MTP activity test. Solubilised liver microsomes from various species (e.g. rat, pig) can be used as the MTP source. To prepare the donor and acceptor vesicles, lipids dissolved in organic solvents were mixed in a suitable ratio and applied to the wall of glass container in a thin layer by blowing the solvent in a nitrogen current. The solution used to prepare donor vesicles contained 400 µM of phosphatidyl choline, 75 µM of cardiolipin and 10 µM of [^{14}C]-triolein (68.8 µCi/mg). To prepare the acceptor vesicles, a solution of 1.2 mM of phosphatidyl choline, 5 µM of triolein and 15 µM of [^{3}H]-dipalmitoyl-phosphatidyl choline (108 mCi/mg) was used. Vesicles are produced by wetting the dried lipids with test buffer and subsequently treating with ultrasound. Vesicle populations of uniform size were obtained by gel filtration of the ultrasound-treated lipids. The MTP activity test contains donor vesicles, acceptor vesicles as well as the MTP source in test buffer. Substances were added from concentrated DMSO-containing stock solutions, the final concentration of DMSO in the test was 0.1%. The reaction was started by the addition of MTP. After a corresponding

incubation time the transfer process was stopped by the addition of 500 µl of a SOURCE 30Q anion exchanger suspension (Pharmacia Biotech). The mixture was shaken for 5 minutes and the donor vesicles bound to the anion exchanger material were separated off by centrifuging. The radioactivity of [^{3}H] and [^{14}C] in the supernatant was determined by liquid scintillation measurement and from this the recovery of the acceptor vesicles and the triglyceride transfer speed was calculated. The compounds of general formula I exhibit IC_{50} values ≤ 100µM in the test described.

In view of the abovementioned biological properties the compounds of general formula I and the physiologically acceptable salts thereof are particularly suitable for lowering the plasma concentration of atherogenic apolipoprotein B (apoB)-containing lipoproteins such as chylomicrons and/or very low density lipoproteins (VLDL) as well as the residues thereof such as low density lipoproteins (LDL) and/or lipoprotein(a) (Lp(a)), for treating hyperlipidaemias, for preventing and treating atherosclerosis and the clinical sequelae thereof, and for preventing and treating related disorders such as diabetes mellitus, adiposity and pancreatitis, oral administration being preferred.

The daily dose needed to achieve such an effect is between 0.5 and 500 mg, expediently between 1 and 350 mg, but preferably between 5 and 200 mg, in adults.

For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances such as other lipid-lowering agents, for example HMG-CoA-reductase-inhibitors, cholesterol biosynthesis inhibitors such as squalene synthase inhibitors and squalene cyclase inhibitors, bile acid-binding resins, fibrates, cholesterol resorption inhibitors, niacin, probucol, CETP inhibitors and ACAT inhibitors together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in

conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention in more detail:

Example 1

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-
3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide

a. 4-(3-methyl-5-phenyl-pyrazol-1-yl)-benzonitrile
A solution of 20.0 g (0.118 mol) of 4-cyanophenylhydrazine and 19.1 g (0.118 mol) of benzoylacetone in 600 ml methanol is combined with 16.7 ml of triethylamine and stirred for two days. The solvent is distilled off, the residue is distributed in dichloromethane/water and the combined organic extracts are dried. The residue is chromatographed on silica gel, eluting with dichloromethane.
Yield: 22.2 g (73% of theory),
R_f value: 0.9 (silica gel; dichloromethane/methanol= 19:1)
$C_{17}H_{13}N_3$ (259.31)
Mass spectrum : $(M+H)^+ = 260$

b. 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine
22.2 g (0.086 mol) of 4-(3-methyl-5-phenyl-pyrazol-1-yl)-benzonitrile are dissolved in 660 ml of methanolic ammonia and after the addition of Raney nickel hydrogenated at ambient temperature with hydrogen. The catalyst is filtered off and the solution is evaporated down. The residue is chromatographed on silica gel, eluting with dichloromethane/methanol = 4:1.
Yield: 22 g (97 % of theory),
R_f value: 0.2 (silica gel; dichloromethane/methanol= 9:1)
$C_{17}H_{17}N_3$ (263.35)
Mass spectrum : $(M+H)^+ = 264$

$M^+ = 263$

c. ethyl 3-(4'-methylbiphenyl-2-carbonylamino)-benzoate

1.6 g (9.9 mmol) of ethyl 3-aminobenzoate are placed in 80 ml of tetrahydrofuran and 2.8 mol (20 mmol) of triethylamine, a solution of 2.3 g (9.9 mmol) of 4'-methylbiphenyl-2-carboxylic acid chloride is added dropwise and the mixture is stirred for 1 more hour. The solvent is distilled off, the residue is distributed in ethyl acetate/water, the combined organic extracts are dried and evaporated down.

Yield: 3.5 g (98 % of theory),

R_f value: 0.7 (silica gel; dichloromethane/methanol= 19:1)

d. 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid

3.5 g (9.7 mmol) of ethyl 4'-methylbiphenyl-2-carbonylamino)-benzoate are stirred in 100 ml methanol and 15 ml of 2 molar sodium hydroxide solution for 1 hour at 50°C. The solvent is distilled off, the residue is combined with water and acidified with 2 molar hydrochloric acid. Precipitated product is suction filtered.

Yield: 3.2 g (99% of theory),

R_f value: 0.2 (silica gel; dichloromethane/methanol= 19:1)

e. 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid chloride

490 mg (1.5 mmol) of 4'-methylbiphenyl-2-carbonylamino)-benzoic acid are stirred in 5 ml thionyl chloride with the addition of 3 drops of dimethylformamide for 1 hour. Then the mixture is evaporated down and the residue is further reacted directly.

Yield: 518 mg (100% of theory).

f. N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide

A mixture of 518 mg (1.5 mmol) of 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid chloride, 390 mg (1.5 mmol) of 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine and 0.7 ml (5 mmol) of triethylamine are stirred in 20 ml tetrahydrofuran for 1 hour. The

solvent is distilled off and the residue chromatographed on silica gel, eluting with dichloromethane/ethanol 0-4 %.

Yield: 340 mg (40% of theory),

R_f value: 0.7 (silica gel; dichloromethane/ethanol = 9:1)

$C_{38}H_{32}N_4O_2$ (576.70)

Mass spectrum : $(M+H)^+$ = 577

$(M-H)^-$ = 575

$(M+Na)^+$ = 599

Example 2

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 47 % of theory,

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)

$C_{38}H_{29}F_3N_4O_2$ (630.67)

Mass spectrum : $(M+H)^+$ = 631

$(M-H)^-$ = 629

$(M+Na)^+$ = 653

Example 3

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 54 % of theory,

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

$C_{37}H_{30}N_4O_2$ (562.67)

Mass spectrum : $(M+H)^+$ = 563

$(M-H)^-$ = 561

$(M+Na)^+$ = 585

Example 4

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-fluorobiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-fluorobiphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 52 % of theory,

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 50:1)

$C_{37}H_{29}FN_4O_2$ (580.66)

Mass spectrum : $(M-H)^-$ = 579

$(M+Na)^+$ = 603

Example 5

N-[4-(N-methyl-N-phenylaminocarbonyl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid chloride and 4-amino-N-methyl-N-phenyl-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 37 % of theory,

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)

$C_{36}H_{28}F_3N_3O_3$ (607.64)

Mass spectrum : $(M+H)^+$ = 608

$(M-H)^-$ = 606

$(M+Na)^+$ = 630

Example 6

N-[4-(N-methyl-N-phenylaminocarbonyl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid chloride and 4-amino-N-methyl-N-phenyl-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 35 % of theory,

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

$C_{35}H_{29}N_3O_3$ (539.64)

Mass spectrum : $(M+H)^+$ = 540

$(M-H)^-$ = 538

$(M+Na)^+$ = 562

Example 7

N-(biphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

A solution of 0.3 g (0.8 mmol) of 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 0.1 g (0.8 mmol) of 4-phenyl-benzylamine and 0.5 ml (4.6 mmol) of N-methylmorpholine in 25 ml of dichloromethane is combined with 0.9 ml (1.6 mmol) of propanephosphonic acid cycloanhydride (50 wt-% in ethyl acetate) at -10°C and stirred for 2 hours while cooling. The mixture is chromatographed on silica gel, eluting with a gradient from 100%-dichloromethane to dichloromethane/methanol/ammonia = 20:77.5:2.5.

Yield: 0.2 g (47 % of theory),

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{25}F_3N_2O_2$ (550.58)

Mass spectrum : $(M-H)^-$ = 549

Example 8

N-(pyridine-3-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-picolylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 81 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{27}H_{20}F_3N_3O_2$ (475.47)

Mass spectrum : $(M-H)^-$ = 474

Example 9

N-(2-phenylethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-phenylethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 60 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{23}F_3N_2O_2$ (488.51)

Mass spectrum : $(M-H)^-$ = 487

Example 10

N-(4-benzoylamino-phenylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-benzoylamino-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 57 % of theory

R_f value: 0.56 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{27}N_3O_3$ (525.61)

Mass spectrum : $(M-H)^-$ = 524

Example 11

N-(2-acetylamino-ethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenylene-2-carbonylamino)-benzoic acid and N-(2-amino-ethyl)-acetamide in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 41 % of theory

R_f value: 0.45 (silica gel; dichloromethane/ethanol = 9:1)

$C_{25}H_{22}F_3N_3O_3$ (469.46)

Mass spectrum : $(M-H)^-$ = 468

Example 12

N-(4-benzoylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-benzoylamino-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 30 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{26}F_3N_3O_3$ (593.61)

Mass spectrum : $(M-H)^-$ = 592

Example 13

N-phenyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and aniline in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 59 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{27}H_{19}F_3N_2O_2$ (460.46)

Mass spectrum : $(M-H)^-$ = 459

$(M+Na)^+$ = 483

Example 14

N-methyl-N-propyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-methyl-propylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 44 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{25}H_{23}F_3N_2O_2$ (440.47)

Mass spectrum : $(M-H)^-$ = 439

Example 15

N-(2-ethoxycarbonylethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and β-alanine ethyl ester in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 11 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{26}H_{23}F_3N_2O_4$ (484.48)

Mass spectrum : $(M-H)^-$ = 483

$(M+Na)^+$ = 507

Example 16

N-tert.butoxycarbonylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and tert.butyl hydrazinoformate in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 46 % of theory

R_f value: 0.58 (silica gel; dichloromethane/ethanol = 9:1)

$C_{26}H_{24}F_3N_3O_4$ (499.49)

Mass spectrum : $(M-H)^-$ = 498

Example 17

N-phenylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and phenylhydrazine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 8 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{27}H_{20}F_3N_3O_2$ (475.47)

Mass spectrum : $(M-H)^-$ = 474

$(M+Na)^+$ = 498

Example 18

N-(N-tert.butoxycarbonyl-piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-tert.butoxy-carbonyl-piperidin-4-yl-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 38 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)

$C_{32}H_{34}F_3N_3O_4$ (581.64)

Mass spectrum : $(M-H)^-$ = 580

$(M+Na)^+$ = 604

Example 19

N-phenylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 46 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)

$C_{28}H_{21}F_3N_2O_2$ (474.49)

Mass spectrum : $(M-H)^-$ = 473

$(M+Na)^+$ = 497

Example 20

N-(biphenyl-2-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-phenyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 65 % of theory

R_f value: 0.74 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{25}F_3N_2O_2$ (550.59)

Mass spectrum : $(M-H)^-$ = 549
$(M+Na)^+$ = 573

Example 21

N-propyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide
Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and propylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 33 % of theory
R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)
$C_{24}H_{21}F_3N_2O_2$ (426.44)
Mass spectrum : $(M-H)^-$ = 425
$(M+Na)^+$ = 449

Example 22

N-ethoxycarbonylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide
Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and glycine ethyl ester hydrochloride in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 79 % of theory
R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)
$C_{25}H_{21}F_3N_2O_4$ (470.45)
Mass spectrum : $(M-H)^-$ = 469
$(M+Na)^+$ = 493

Example 23

N-dimethylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N,N-dimethylhydrazine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 57 % of theory

R_f value: 0.85 (silica gel; dichloromethane/ethanol = 9:1)

$C_{23}H_{20}F_3N_3O_2$ (427.43)

Mass spectrum : $(M-H)^-$ = 426

$(M+H)^+$ = 428

$(M+Na)^+$ = 450

Example 24

N-phenylmethyl-N-methyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-methyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 95 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{23}F_3N_2O_2$ (488.51)

Mass spectrum : $(M-H)^-$ = 487

$(M+Na)+$ = 511

Example 25

N-[4-(phenylmethyl)-phenyl]-3-(4-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 4'-methylbiphenyl-2-carboxylic acid chloride and 3-amino-N-(4-benzyl-phenyl)-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 83 % of theory,

R_f value: 0.6 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

Example 26

N-(biphenyl-3-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-phenylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 58 % of theory

R_f value: 0.71 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{25}F_3N_2O_2$ (550.59)

Mass spectrum : $(M-H)^-$ = 549

$(M+Na)^+$ = 573

Example 27

N-[4-(1H-imidazol-2-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide-hydrochloride

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid and 4-(1H-imidazol-2-yl)benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 96 % of theory

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 95:5)

$C_{30}H_{24}N_4O_2$ x HCl (472.54/509.01)

Mass spectrum : $(M+H)^+$ = 473

Example 28

N-(biphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid and 4-phenylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 88 % of theory

R_f value: 0.76 (silica gel; dichloromethane/ethanol = 95:5)

$C_{33}H_{26}N_2O_2$ (482.59)

Mass spectrum : $(M-H)^-$ = 481

$(M+H)^+$ = 483

$(M+Na)^+$ = 505

Example 29

N-(4'-hydroxybiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(4-hydroxyphenyl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 6 % of theory

R_f value: 0.88 (silica gel; dichloromethane/ethanol = 95:5)

$C_{33}H_{26}N_2O_3$ (498.59)

Mass spectrum : $(M-H)^-$ = 497

$(M+Cl)^-$ = 533/35 (chlorine isotopes)

Example 30

N-(piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide-trifluoroacetate

0.2 g (0.27 mmol) of N-(N-tert.butoxycarbonyl-piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide are stirred in 30 ml dichloromethane and 3 ml of trifluoroacetic acid for 17 hours at ambient temperature. Then the mixture is evaporated to dryness *in vacuo*.

Yield: 0.2 g (98 % of theory),

R_f value: 0.42 (silica gel; dichloromethane/ethanol = 9:1)

$C_{27}H_{26}F_3N_3O_2$ x CF_3COOH (481.52/595.55)

Mass spectrum : $(M+H)^+$ = 482

Example 31

N-[N-(N-methyl-N-phenylaminocarbonyl)-piperidin-4-yl-methyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide-trifluoroacetate and N-methyl-N-phenyl-carbamoylchloride in tetrahydrofuran with the addition of triethylamine.

Yield: 99 % of theory,

R_f value: 0.57 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{33}F_3N_4O_3$ (614.67)

Mass spectrum : $(M-H)^-$ = 613

Example 32

N-[4-(3-methyl-5-tert.butyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(5-tert.-butyl-3-methyl-pyrazol-1-yl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 53 % of theory

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)

$C_{36}H_{33}F_3N_4O_2$ (610.69)

Mass spectrum : $(M-H)^-$ = 609

$(M+H)^+$ = 611

$(M+Na)^+$ = 633

Example 33

N-methyl-N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1c from 4'-methylbiphenyl-2-carboxylic acid chloride and N-methyl-N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-amino-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 22 % of theory

R_f value: 0.6 (silica gel; dichloromethane/methanol= 9:1)

$C_{39}H_{34}N_4O_2$ (590.73)

Mass spectrum : $(M-H)^-$ = 589

$(M+H)^+$ = 591

Example 34

N-(pyridine-3-yl-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

3.2 mg (10 µmol) of 3-(biphenyl-2-carbonylamino)-benzoic acid are placed in 0.4 ml dimethylformamide and after the addition of 1.6 mg (15 µmol) of 3-picolylamine, 3.9 mg (12 µmol) of O-(benzo-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and 7 mg (50 µmol) of N-ethyl-diisopropylamine the mixture is stirred for 12 hours. The solution is evaporated down.

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 19:1)

$C_{26}H_{21}N_3O_2$ (407.47)

Mass spectrum : $(M+H)^+$ = 408

Example 35

N-phenyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, aniline, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 19:1)

$C_{26}H_{20}N_2O_2$ (392.46)

Mass spectrum : $(M+Na)^+$ = 415

Example 36

N-tert.butyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid, tert.butylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

$C_{24}H_{24}N_2O_2$ (372.47)

Mass spectrum : $(M+Na)^+$ = 395

Example 37

N-hydroxyethyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 2-aminoethanol, TBTU and N-ethyl-diisopropylamine in dimethylformamide.

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 19:1)

$C_{22}H_{20}N_2O_3$ (360.41)

Mass spectrum : $(M+Na)^+$ = 383

Example 38

N-(2-dimethylamino-ethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, N,N-dimethylethylenediamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

$C_{24}H_{25}N_3O_2$ (387.48)

Mass spectrum : $(M+H)^+$ = 388

M^+ = 387

Example 39

N-(2-carboxy-ethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide-sodium salt

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, β-alanine, TBTU, sodium hydroxide solution and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 9:1)

$C_{23}H_{19}NaN_2O_4$ (410.41), free acid $C_{23}H_{20}N_2O_4$ (388.42)

Mass spectrum : $(M-H)^-$ = 387

Example 40

N-(4-[1,2,3]-thiadiazol-4-yl-phenylmethyl)-3-(4'-trifluoro-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-[1,2,3]-thiadiazol-4-yl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 18 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{30}H_{21}F_3N_4O_2S$ (558.58)

Mass spectrum : $(M-H)^-$ = 557

$(M+H)^+$ = 559

$(M+Na)^+$ = 581

Example 41

N-(4-phenylaminosulphonyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-aminomethyl-N-phenyl-benzenesulphonamide in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 73 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{26}F_3N_3O_4S$ (629.66)

Mass spectrum : $(M-H)^-$ = 628

$(M+H)^+$ = 630

$(M+Na)^+$ = 652

Example 42

N-(4-piperidin-1-yl-phenylmethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-piperidin-1-yl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 47 % of theory

R_f value: 0.69 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{30}F_3N_3O_2$ (557.61)

Mass spectrum : $(M-H)^-$ = 556

$(M+Na)^+$ = 580

Example 43

N-(4-phenylsulphonylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-phenylsulphonylamino-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 57 % of theory

R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{26}F_3N_3O_4S$ (629.66)

Mass spectrum : $(M-H)^-$ = 628

$(M+H)^+$ = 630

$(M+Na)^+$ = 652

Example 44

N-[4-(2-methyl-pyrrol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(2-methyl-pyrrol-1-yl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 22 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{26}F_3N_3O_2$ (553.58)

Mass spectrum : $(M-H)^-$ = 552

$(M+H)^+$ = 554

$(M+Na)^+$ = 576

Example 45

N-(2'-methylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(2-methylphenyl)benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 21 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{27}F_3N_2O_2$ (564.60)

Mass spectrum : $(M-H)^-$ = 563

$(M+Na)^+$ = 587

Example 46

N-(4-tert.butyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-tert.butyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 53 % of theory

R_f value: 0.69 (silica gel; dichloromethane/ethanol = 9:1)

$C_{32}H_{29}F_3N_2O_2$ (530.59)

Mass spectrum : $(M-H)^-$ = 529

$(M+Na)^+$ = 553

Example 47

N-(4-isopropyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-isopropylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 58 % of theory

R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)

$C_{31}H_{27}F_3N_2O_2$ (516.56)

Mass spectrum : $(M-H)^-$ = 515

$(M+Na)^+$ = 539

Example 48

N-(4-Bromophenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-bromobenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 51 % of theory

R_f value: 0.64 (silica gel; dichloromethane/ethanol = 9:1)

$C_{28}H_{20}BrF_3N_2O_2$ (553.38)

Mass spectrum : $(M-H)^-$ = 551/53 (bromine isotopes)

$(M+Na)^+$ = 575/77 (bromine isotopes)

Example 49

N-(4-trifluoromethyl-phenylmethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-trifluoromethyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 48 % of theory

R_f value: 0.63 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{20}F_6N_2O_2$ (542.48)

Mass spectrum : $(M-H)^-$ = 541

$(M+Na)^+$ = 565

Example 50

N-(4-acetylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-acetylaminobenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 38 % of theory

R_f value: 0.60 (silica gel; dichloromethane/ethanol = 9:1)

$C_{30}H_{24}F_3N_3O_3$ (531.53)

Mass spectrum : $(M+Na)^+$ = 554

Example 51

N-(1H-benzimidazol-2-yl-methyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-(aminomethyl)-benzimidazole in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 19 % of theory

R_f value: 0.58 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{21}F_3N_4O_2$ (514.51)

Mass spectrum : $(M-H)^-$ = 513

$(M+H)^+$ = 515

Example 52

N-(4'-methylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(4'-methylphenyl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 21 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{27}F_3N_2O_2$ (564.61)

Mass spectrum : $(M-H)^-$ = 563

$(M+Na)^+$ = 587

Example 53

N-(4-methyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-methylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 82 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{23}F_3N_2O_2$ (488.51)

Mass spectrum : $(M-H)^-$ = 487

$(M+Na)^+$ = 511

Example 54

N-(biphenyl-4-methyl)-2-methyl-5-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1c from biphenyl-2-carboxylic acid chloride and N-(biphenyl-4-methyl)-2-methyl-5-amino-benzoic acid amide in tetrahydrofuran and triethylamine.

Yield: 92 % of theory

R_f value: 0.74 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

$(M+Na)^+$ = 519

Example 55

N-(biphenyl-4-methyl)-4-methyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-4-methyl-benzoic acid and biphenyl-4-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 30 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

Example 56

N-(Naphthalin-2-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and naphthalin-2-yl-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 50 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol= 9:1)

$C_{32}H_{23}F_3N_2O_2$ (524.54)

Mass spectrum : $(M-H)^-$ = 523

$(M+H)^+$ = 525

$(M+Na)^+$ = 547

Example 57

N-[4-(N-Methyl-N-cyclohexyl-aminocarbonyl)-phenylmethyl]-3- (biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(N-methyl-N-cyclohexyl-aminocarbonyl)-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 72 % of theory

R_f value: 0.61 (silica gel; dichloromethane/ethanol= 9:1)

$C_{35}H_{35}N_3O_3$ (545.68)

Mass spectrum : $(M-H)^-$ = 544

$(M+Na)^+$ = 568

Example 58

N-[4-(N-methyl-N-phenylcarbonyl-amino)-phenylmethyl]-3- (biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(N-methyl-N-phenylcarbonyl-amino)-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 37 % of theory

R_f value: 0.59 (silica gel; dichloromethane/ethanol= 9:1)

$C_{35}H_{29}N_3O_3$ (539.64)

Mass spectrum : $(M-H)^-$ = 538

$(M+H)^+$ = 540

$(M+Na)^+$ = 562

Example 59

N-(4-bromo-phenylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 4-bromo-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 100 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol= 9:1)

$C_{27}H_{21}BrN_2O_2$ (485.38)

Mass spectrum : $(M+ Na)^+$ = 507/509 (bromine isotopes)

Example 60

N-(1H-Benzimidazol-5-ylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and (1H-benzimidazol-5-yl)-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 93 % of theory

R_f value: 0.65 (silica gel; dichloromethane/ethanol= 9:1)

$C_{29}H_{21}F_3N_4O_2$ (514.51)

Mass spectrum : $(M-H)^-$ = 513

$(M+Na)^+$ = 537

Example 61

N-(4'-methylbiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(4-methylphenyl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 47 % of theory

R_f value: 0.7 (silica gel; dichloromethane/ethanol= 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

$(M+Na)^+$ = 519

Example 62

N-(2'-tert.Butoxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(2-tert.butoxyphenyl)benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 46 % of theory

R_f value: 0.81 (silica gel; dichloromethane/ethanol= 9:1)

$C_{39}H_{33}F_3N_2O_4$ (650.70)

Mass spectrum : $(M-H)^-$ = 649

$(M+Na)^+$ = 673

Example 63

N-(2'-Hydroxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 30 from N-(2'-tert.butoxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and trifluoroacetic acid in dichloromethane.

Yield: 95 % of theory

R_f value: 0.64 (silica gel; dichloromethane/ethanol= 9:1)

$C_{35}H_{25}F_3N_2O_4$ (594.59)

Mass spectrum : $(M-H)^-$ = 593

Example 64

N-(4-Aminophenyl)methyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide-hydrochloride

Prepared analogously to Example 34 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid, 4-amino-benzylamine, TBTU and N-ethyl-diisopropylamine in dimethylformamide and subsequent treatment with dilute HCl.

Yield: 24 % of theory

R_f value: 0.28 (silica gel; dichloromethane/ethanol= 9.5:0.5)

$C_{28}H_{22}F_3N_3O_2$ x HCl (489.50/525.96)

Mass spectrum : $(M-H)^-$ = 488

$(M+Na)^+$ = 512

$(M+Cl)^-$ = 524/26 (chlorine isotopes)

Example 65

N-[4-(N-methyl-N-cyclohexylcarbonyl-amino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(N-methyl-N-cyclohexylcarbonyl-amino)-benzylamine in

dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 49 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol= 9:1)

$C_{36}H_{34}F_3N_3O_3$ (613.68)

Mass spectrum : $(M-H)^-$ = 612

Example 66

N-(1-Phenyl-piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and (1-phenyl-piperidin-4-yl)-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 50 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol= 9:1)

$C_{33}H_{30}F_3N_3O_2$ (557.62)

Mass spectrum : $(M-H)^-$ = 556

$(M+Na)^+$ = 580

Example 67

N-[3-methyl-4-(phenylcarbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-methyl-4-(phenylcarbonylamino)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 89 % of theory

R_f value: 0.66 (silica gel; dichloromethane/ethanol= 9:1)

$C_{36}H_{28}F_3N_3O_3$ (607.63)

Mass spectrum : $(M-H)^-$ = 606

Example 68

N-(4-Cyclohexylcarbonylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and cyclohexanecarboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 6 % of theory

R_f value: 0.87 (silica gel; dichloromethane/ethanol= 4:1)

$C_{35}H_{32}F_3N_3O_3$ (599.65)

Mass spectrum : $(M-H)^-$ = 598

Example 69

N-(4-tert.butoxycarbonylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pivalic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 46 % of theory

R_f value: 0.78 (silica gel; dichloromethane/ethanol= 4:1)

$C_{33}H_{30}F_3N_3O_3$ (573.62)

Mass spectrum : $(M-H)^-$ = 572

Example 70

N-(naphthalin-1-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 1-aminomethyl-naphthaline in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 53 % of theory

R_f value: 0.70 (silica gel; dichloromethane/ethanol= 9:1)

$C_{32}H_{23}F_3N_2O_2$ (524.54)

Mass spectrum : $(M-H)^-$ = 523

$(M+Na)^+$ = 547

Example 71

N-(3-phenyl-prop-2-in-ylamino)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-phenyl-prop-2-ynylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 54 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol= 9:1)

$C_{30}H_{21}F_3N_2O_2$ (498.51)

Mass spectrum : $(M-H)^-$ = 497

$(M+Na)^+$ = 521

Example 72

N-(biphenyl-4-methyl)-N-methyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-methyl-4-phenylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 92 % of theory

R_f value: 0.70 (silica gel; dichloromethane/ethanol= 9:1)

$C_{35}H_{27}F_3N_2O_2$ (564.61)

Mass spectrum : $(M-H)^-$ = 563

Example 73

N-(biphenyl-4-methyl)-3-(6-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 6-methyl-biphenyl-2-carboxylic acid and N-(biphenyl-4-methyl)-3-amino-benzoic acid amide in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 19 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol= 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

$(M+Na)^+$ = 519

Example 74

N-[4-(Pyridin-3-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and nicotinic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 39 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol= 4:1)

$C_{34}H_{25}F_3N_4O_3$ (594.59)

Mass spectrum : $(M-H)^-$ = 593

Example 75

N-(4-Butylcarbonylamino-phenylmethyl)-3-(4'-trifluoromethylbi-phenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and valeric acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 79 % of theory

R_f value: 0.77 (silica gel; dichloromethane/ethanol= 4:1)

$C_{33}H_{30}F_3N_3O_3$ (573.62)

Mass spectrum : $(M-H)^-$ = 572

$(M+Na)^+$ = 596

Example 76

N-(4-Dimethylamino-phenylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 4-dimethylamino-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 100 % of theory

R_f value: 0.35 (silica gel; dichloromethane/ethanol= 19:1)

$C_{29}H_{27}N_3O_2$ (449.55)

Mass spectrum : $(M-H)^-$ = 448

$(M+Na)^+$ = 472

Example 77

N-[4-(Pyridin-4-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and isonicotinic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 40 % of theory,

R_f value: 0.78 (silica gel; dichloromethane/ethanol= 4:1)

$C_{34}H_{25}F_3N_4O_3$ (594.59)

Mass spectrum : $(M-H)^-$ = 593

$(M+H)^+$ = 595

Example 78

N-(2'-methylaminocarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(2'-hydroxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 7 % of theory

R_f value: 0.43 (silica gel; dichloromethane/ethanol= 95:5)

$C_{36}H_{28}F_3N_3O_3$ (607.64)

Mass spectrum : $(M-H)^-$ = 606

$(M+Na)^+$ = 630

Example 79

N-[4-(Pyrrolidin-1-yl-carbonylamino)-phenylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyrrolidin-1-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 81 % of theory,

R_f value: 0.45 (silica gel; dichloromethane/ethanol= 9:1)

$C_{33}H_{29}F_3N_4O_3$ (586.62)

Mass spectrum : $(M-H)^-$ = 585

Example 80

N-[4-(4-methyl-piperazin-1-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 4-(4-methyl-piperazin-1-yl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.20 (silica gel; dichloromethane/ethanol= 9:1)

$C_{32}H_{32}N_4O_2$ (504.63)

Mass spectrum : $(M-H)^-$ = 503

$(M+H)^+$ = 505

$(M+Na)^+$ = 527

Example 81

N-(4-phenylcarbonylamino-phenylmethyl)-3-(6-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 6-methyl-biphenyl-2-carboxylic acid chloride and N-(4-phenylcarbonylamino-phenylmethyl)-3-amino-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 85 % of theory

R_f value: 0.40 (silica gel; dichloromethane/ethanol= 19:1)

$C_{35}H_{29}N_3O_3$ (539.64)

Mass spectrum : $(M-H)^-$ = 538

$(M+Na)^+$ = 562

Example 82

N-[4-(pyrrolidin-1-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 4-(pyrrolidin-1-yl)-phenylmethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.70 (silica gel; dichloromethane/ethanol= 9:1)

$C_{31}H_{29}N_3O_2$ (475.59)

Mass spectrum : $(M-H)^-$ = 474

$(M+H)^+$ = 476

$(M+Na)^+$ = 498

Example 83

N-[4-(2-methyl-phenylcarbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-aminophenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and 2-tolylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 71 % of theory

R_f value: 0.55 (silica gel; dichloromethane/ethanol= 9:1)

$C_{36}H_{28}F_3N_3O_3$ (607.63)

Mass spectrum : $(M-H)^-$ = 606

$(M+Na)^+$ = 630

Example 84

N-[4-(4-methyl-phenylcarbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-aminophenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and 4-tolylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 95 % of theory

R_f value: 0.56 (silica gel; dichloromethane/ethanol= 9:1)

$C_{36}H_{28}F_3N_3O_3$ (607.63)

Mass spectrum : $(M-H)^-$ = 606

$(M+Na)^+$ = 630

Example 85

N-(2'-dimethylaminocarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(2'-hydroxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and dimethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 24 % of theory

R_f value: 0.41 (silica gel; dichloromethane/ethanol= 95:5)

$C_{37}H_{30}F_3N_3O_3$ (621.66)

Mass spectrum : $(M-H)^-$ = 620

$(M+Na)^+$ = 644

Example 86

N-(2'-pyrrolidin-1-yl-carbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(2'-hydroxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyrrolidine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 92 % of theory

R_f value: 0.44 (silica gel; dichloromethane/ethanol= 95:5)

$C_{39}H_{32}F_3N_3O_3$ (647.70)

Mass spectrum : $(M-H)^-$ = 646

$(M+Na)^+$ = 670

Example 87

N-[2'(2,2,2-trifluorethyl-aminocarbonyl)-biphenyl-4-methyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(2'-hydroxycarbonylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and 2,2,2-trifluoroethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 18 % of theory

R_f value: 0.41 (silica gel; dichloromethane/ethanol= 95:5)

$C_{37}H_{27}F_6N_3O_3$ (675.63)

Mass spectrum : $(M-H)^-$ = 674

$(M+Na)^+$ = 698

Example 88

N-[4-(Pyridin-2-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-aminophenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyridin-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 74 % of theory

R_f value: 0.64 (silica gel; dichloromethane/ethanol= 9:1)

$C_{34}H_{25}F_3N_4O_3$ (594.59)

Mass spectrum : $(M-H)^-$ = 593

$(M+H)^+$ = 595

$(M+Na)^+$ = 617

Example 89

N-(4'-methylbiphenyl-4-methyl)-2-methyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4'-methylbiphenyl-4-methyl)-3-amino-2-methyl-benzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 22 % of theory

R_f value: 0.79 (silica gel; dichloromethane/ethanol= 9:1)

$C_{35}H_{30}N_2O_2$ (510.64)

Mass spectrum : $(M-H)^-$ = 509

$(M+Na)^+$ = 533

Example 90

N-(biphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-5-nitro-benzoic acid amide

Prepared analogously to Example 1f from N-(biphenyl-4-methyl)-3-amino-5-nitro-benzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 55 % of theory

R_f value: 0.88 (silica gel; dichloromethane/ethanol= 9:1)

$C_{33}H_{25}N_3O_4$ (527.58)

Mass spectrum : $(M-H)^-$ = 526

$(M+Na)^+$ = 550

Example 91

N-(biphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-5-methyl-benzoic acid amide

Prepared analogously to Example 1f from N-(biphenyl-4-methyl)-3-amino-5-methyl-benzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 5 % of theory

R_f value: 0.80 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{28}N_2O_2$ (496.61)

Mass spectrum : $(M-H)^-$ = 495

$(M+Na)^+$ = 519

Example 92

N-(biphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-4-fluor-benzoic acid amide
Prepared analogously to Example 1f from N-(biphenyl-4-methyl)-3-amino-4-fluorobenzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.
Yield: 100 % of theory
R_f value: 0.45 (silica gel; dichloromethane)
$C_{33}H_{25}FN_2O_2$ (500.57)
Mass spectrum : $(M-H)^-$ = 499
$(M+Na)^+$ = 523

Example 93

N-(biphenyl-4-methyl)-5-amino-3-(biphenyl-2-carbonylamino)- benzoic acid amide
60 mg (0.11 mmol) of N-(biphenyl-4-methyl)-5-nitro-3-(biphenyl-2-carbonylamino)-benzoic acid amide are dissolved in 20 ml of methanol and 10 ml of dichloromethane and after the addition of 16 mg of palladium on activated charcoal (20 %) hydrogenated with hydrogen for 3 hours at ambient temperature. The catalyst is filtered off and the solution is evaporated down.
Yield: 56 mg (100 % of theory),
R_f value: 0.56 (silica gel; dichloromethane/ethanol = 9:1)
$C_{33}H_{27}N_3O_2$ (497.60)
Mass spectrum : $(M-H)^-$ = 496
$(M+H)^+$ = 498
$(M+Na)^+$ = 520

Example 94

N-(biphenyl-4-methyl)-5-(biphenyl-2-carbonylamino)-2-fluoro- benzoic acid amide

Prepared analogously to Example 1f from N-(biphenyl-4-methyl)-5-amino-2-fluorobenzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 64 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{25}FN_2O_2$ (500.57)

Mass spectrum : $(M-H)^-$ = 499

$(M+Na)^+$ = 523

Example 95

N-[4-(pyrazin-2-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyrazin-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 22 % of theory

R_f value: 0.95 (silica gel; dichloromethane/ethanol = 8:2)

$C_{33}H_{24}F_3N_5O_3$ (595.58)

Mass spectrum : $(M-H)^-$ = 594

$(M+Na)^+$ = 618

Example 96

N-[4-(pyrimidin-4-yl-carbonylamino)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyrimidine-4-carboxylic acid in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 29 % of theory

R_f value: 0.35 (silica gel; petroleum ether/ethyl acetate = 3:7)

$C_{33}H_{24}F_3N_5O_3$ (595.58)

Mass spectrum : $(M-H)^-$ = 594

$(M+Na)^+$ = 618

Example 97

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(6-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-amino-benzoic acid amide and 6-methylbiphenyl-2-carboxylic acid chloride in dimethylformamide with the addition of triethylamine.

Yield: 24 % of theory

R_f value: 0.20 (silica gel; petroleum ether/ethyl acetate = 1:1)

$C_{38}H_{32}N_4O_2$ (576.70)

Mass spectrum : $(M-H)^-$ = 575

$(M+H)^+$ = 577

$(M+Na)^+$ = 599

Example 98

N-[3-(4-methylphenyl)-prop-2-ynyl]-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-(4-methylphenyl)-prop-2-ynyl-amine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 24 % of theory

R_f value: 0.45 (silica gel; dichloromethane/ethanol = 95:5)

$C_{31}H_{23}F_3N_2O_2$ (512.53)

Mass spectrum : $(M-H)^-$ = 511

$(M+Na)^+$ = 535

Example 99

N-[3-(4-Isopropylphenyl)-prop-2-ynyl]-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-(4-isopropylphenyl)-prop-2-ynyl-amine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 46 % of theory

R_f value: 0.43 (silica gel; dichloromethane/ethanol = 95:5)

$C_{33}H_{27}F_3N_2O_2$ (540.59)

Mass spectrum : $(M-H)^-$ = 539

$(M+Na)^+$ = 563

Example 100

N-(biphenyl-4-methyl)-N-methyl-5-(biphenyl-2-carbonylamino)-2-methyl-benzoic acid amide

Prepared analogously to Example 1f from N-(biphenyl-4-methyl)-N-methyl-5-amino-2-methyl-benzoic acid amide and biphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 72 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 19:1)

$C_{35}H_{30}N_2O_2$ (510.64)

Mass spectrum : $(M-H)^-$ = 509

$(M+Na)^+$ = 533

Example 101

N-(4-phenylamino-phenylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-phenylamino-benzylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 57 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{27}N_3O_2$ (497.60)

Mass spectrum : $(M+Na)^+$ = 520

M^+ = 497

Example 102

N-(4-Morpholin-4-yl-phenylmethyl)-3-(biphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(morpholin-4-yl)-benzylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 27 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 9:1)

$C_{31}H_{29}N_3O_3$ (491.59)

Mass spectrum : $(M+Na)^+$ = 514

$(M-H)^-$ = 490

M^+ = 491

Example 103

N-[4-(5-methylpyrazin-2-yl-carbonylamino]-phenylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and 5-methylpyrazine-2-carboxylic acid in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 32 % of theory

R_f value: 0.14 (silica gel; petroleum ether/ethyl acetate = 2:3)

$C_{34}H_{26}F_3N_5O_3$ (609.61)

Mass spectrum : $(M-H)^-$ = 608

Example 104

N-[4-(1H-pyrrol-2-yl-carbonylamino]-phenylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and pyrrol-2-carboxylic acid in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 14 % of theory

R_f value: 0.32 (silica gel; petroleum ether/ethyl acetate = 2:3)

$C_{33}H_{25}F_3N_4O_3$ (582.58)

Mass spectrum : $(M-H)^-$ = 581

Example 105

N-[3-(4-isopropylphenyl)-prop-2-ynyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 3-(4-isopropylphenyl)-prop-2-ynyl-amine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 41 % of theory

R_f value: 0.42 (silica gel; dichloromethane/ethanol = 95:5)

$C_{32}H_{28}N_2O_2$ (472.59)

Mass spectrum : $(M-H)^-$ = 471

$(M+Na)^+$ = 495

Example 106

N-[4-(N-methylpyrrol-2-yl)-carbonylaminophenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-amino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and N-methylpyrrol-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 58 % of theory

R_f value: 0.43 (silica gel; petroleum ether/ethyl acetate = 2:3)

$C_{34}H_{27}F_3N_4O_3$ (596.61)

Mass spectrum : $(M+Na)^+$ = 619

M^+ = 596

Example 107

N-(4'-methylbiphenyl-4-methyl)-3-(4'-fluorobiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4'-methylbiphenyl-4-methyl)-3-amino-benzoic acid amide and 4'-fluorobiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 74 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 19:1)

$C_{34}H_{27}FN_2O_2$ (514.60)

Mass spectrum : $(M-H)^-$ = 513

$(M+Na)^+$ = 537

Example 108

N-(4'-trifluoromethylbiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid chloride and 4-(4-trifluoromethylphenyl)-benzylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 46 % of theory

R_f value: 0.65 (silica gel; dichloromethane/ethanol= 9:1)

$C_{34}H_{25}F_3N_2O_2$ (550.58)

Mass spectrum : $(M-H)^-$ = 549

Example 109

N-(4'-fluorobiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 4-(4-fluorophenyl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 89 % of theory

R_f value: 0.40 (silica gel; dichloromethane/ethanol= 19:1)

$C_{33}H_{25}FN_2O_2$ (500.57)

Mass spectrum : $(M-H)^-$ = 499

$(M+Na)^+$ = 523

Example 110

N-[4-(pyridin-4-yl)-phenylmethyl]-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid, 4-(pyridin-4-yl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 79 % of theory

R_f value: 0.5 (silica gel; dichloromethane/ethanol= 9:1)

$C_{33}H_{24}F_3N_3O_2$ (551.57)

Mass spectrum : $(M-H)^-$ = 550

Example 111

N-(4'-Chlorobiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid, 4-(4-chlorophenyl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 75 % of theory

R_f value: 0.0.6 (silica gel; dichloromethane/ethanol= 9:1)

$C_{34}H_{24}ClF_3N_2O_2$ (585.03)

Mass spectrum : $(M-H)^-$ = 583/585 (chlorine isotopes)

Example 112

N-[3-(4-isopropylphenyl)propyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 93 from N-[3-(4-isopropylphenyl)-prop-2-ynyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide and palladium on activated charcoal in ethanol.

Yield: 99 % of theory

R_f value: 0.35 (silica gel; petroleum ether/ethyl acetate = 3:2)

$C_{33}H_{31}F_3N_2O_2$ (544.62)

Mass spectrum : $(M-H)^-$ =543

$(M+Na)^+$ =567

Example 113

N-{4-[N-methyl-N-(3-methylphenyl)amino]-phenylmethyl}-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-{4-[N-methyl-N-(3'-methylphenyl)amino]-phenylmethyl}-3-amino-benzoic acid amide and 4'-trifluoromethylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 32 % of theory

R_f value: 0.60 (silica gel; dichloromethane/methanol = 9:1)

$C_{36}H_{30}F_3N_3O_2$ (593.65)

Mass spectrum : $(M-H)^-$ = 592

$(M+Na)^+$ = 616

Example 114

N-[4-(1,2,3,4-tetrahydroquinolin-1-yl)-phenylmethyl]-3-(4'-fluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-[4-(1,2,3,4-tetrahydroquinolin-1-yl)-phenylmethyl]-3-amino-benzoic acid amide and 4'-fluoromethylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 82 % of theory

R_f value: 0.80 (silica gel; dichloromethane/ethanol = 9:1)

$C_{36}H_{30}FN_3O_2$ (555.65)

Mass spectrum : $(M-H)^-$ = 554

$(M+Na)^+$ = 578

Example 115

N-[4-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-[4-(3,5-dimethyl-4-propyl-pyrazol-1-yl)-phenylmethyl]-3-amino-benzoic acid amide and 4'-trifluoromethylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 66 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 9:1)

$C_{36}H_{33}F_3N_4O_2$ (610.68)

Mass spectrum : $(M-H)^-$ = 609

$(M+H)^+$ = 611

$(M+Na)^+$ = 633

Example 116

N-[4-(Imidazo-[1,2-a]pyridin-2-yl) phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-[4-(imidazo-[1,2-a]pyridin-2-yl)phenylmethyl]-3-amino-benzoic acid amide and 4'-trifluoromethylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 35 % of theory

R_f value: 0.65 (silica gel; dichloromethane/methanol = 9:1)

$C_{35}H_{25}F_3N_4O_2$ (590.60)

Mass spectrum : $(M-H)^-$ = 589

$(M+H)^+$ = 591

$(M+Na)^+$ = 613

Example 117

N-[4-(1,2,3,4-tetrahydroquinolin-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-[4-(1,2,3,4-tetrahydro-quinolin-1-yl)-phenylmethyl]-3-amino-benzoic acid amide and 4'-trifluoromethylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 60 % of theory

R_f value: 0.30 (silica gel; dichloromethane/ethanol = 50:1)

$C_{37}H_{30}F_3N_3O_2$ (605.66)

Mass spectrum : $(M-H)^-$ = 604

$(M+Na)^+$ = 628

Example 118

N-[4-(1-methylbenzimidazol-2-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 4-(1-methylbenzimidazol-2-yl)-benzylamine and 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 31 % of theory

R_f value: 0.70 (silica gel; dichloromethane/ethanol = 19:1)

$C_{36}H_{27}F_3N_4O_2$ (604.63)

Mass spectrum : $(M-H)^-$ = 603

$(M+H)^+$ = 605

$(M+Na)^+$ = 627

Example 119

N-(4-phenylcarbonylphenyl)-3-(4'-methylbiphenylcarbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(4-phenylcarbonylphenyl)-3-amino-benzoic acid amide and 4'-methylbiphenyl-2-carboxylic acid chloride in tetrahydrofuran with the addition of triethylamine.

Yield: 90 % of theory

R_f value: 0.40 (silica gel; dichloromethane/ethanol = 19:1)

$C_{34}H_{26}N_2O_3$ (510.59)

Mass spectrum : $(M-H)^-$ = 509

$(M+H)^+$ = 511

$(M+Na)^+$ = 533

Example 120

N-(4-phenylaminocarbonylamino-phenylmethyl)-3-(4'-trifluoro-methylbiphenyl-2-carbonylamino)-benzoic acid amide

500 mg (0.95 mMol) of N-(4-amino-phenylmethyl)-3-(4'-trifluoro-methylbiphenyl-2-carbonylamino)-benzoic acid amide hydrochloride, 0.1 ml (1.05 mmol) of

phenylisocyanate and 0.3 ml (2.3 mmol) of triethylamine are refluxed in 20 ml of tetrahydrofuran for 3 hours. The solvent is distilled off, the residue is dissolved in ethyl acetate and washed with 2 molar hydrochloric acid and 5 % sodium hydrogen carbonate solution. The combined organic extracts are dried and evaporated down. The crude product is chromatographed on silica gel, eluting with dichloromethane/ethanol (1-3 %).

Yield: 97 mg (17 % of theory),

R_f value: 0.29 (silica gel; dichloromethane/ethanol = 95:5)

$C_{35}H_{27}F_3N_4O_3$ (608.62)

Mass spectrum : $(M-H)^-$ = 607

$(M+Na)^+$ = 631

Example 121

N-(ethoxycarbonylmethyl-aminocarbonylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, glycylglycine ethylester, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 79 % of theory

R_f value: 0.49 (silica gel; petroleum ether/ethyl acetate = 3:2)

$C_{27}H_{24}F_3N_3O_5$ (527.50)

Mass spectrum : $(M-H)^-$ = 526

$(M+H)^+$ = 528

$(M+Na)^+$ = 550

Example 122

N-(biphenyl-4-methyl)-3-(9-oxofluorene-4-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-amino-N-(biphenyl-4-methyl)-benzoic acid amide, 9-oxofluorene-4-carboxylic acid, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 33 % of theory

R_f value: 0.37 (silica gel; dichloromethane/ethanol = 95:5)

$C_{34}H_{24}N_2O_3$ (508.58)

Mass spectrum : $(M-H)^-$ = 507

$(M+Na)^+$ = 531

Example 123

N-(2-methyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 2-methylbenzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 82 % of theory

R_f value: 0.54 (silica gel; dichloromethane/ethanol= 9:1)

$C_{29}H_{23}F_3N_2O_2$ (488.51)

Mass spectrum : $(M-H)^-$ = 487

$(M+H)^+$ = 489

$(M+Na)^+$ = 511

Example 124

N-[4-(6-methylpyridazin-3-yl)-phenylmethyl]-3-(4'-trifluoro-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 4-(6-methylpyridazin-3-yl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 36 % of theory

R_f value: 0.7 (silica gel; dichloromethane/ethanol= 9:1)

$C_{33}H_{25}F_3N_4O_2$ (566.58)

Mass spectrum : $(M-H)^-$ = 565

$(M+H)^+$ = 567

Example 125

N-(2-Difluoromethoxy-phenylmethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 2-difluoromethoxybenzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 80 % of theory

R_f value: 0.69 (silica gel; dichloromethane/ethanol= 19:1)

$C_{29}H_{21}F_5N_2O_3$ (540.49)

Mass spectrum : $(M-H)^-$ = 539

$(M+H)^+$ = 541

$(M+Na)^+$ = 563

Example 126

N-Cyclohexylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, aminomethylcyclohexane, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 87 % of theory

R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)

$C_{28}H_{27}F_3N_2O_2$ (480.53)

Mass spectrum : $(M-H)^-$ = 479

$(M+H)^+$ = 481

$(M+Na)^+$ = 503

Example 127

N-(9-fluorenyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 9-aminofluorene-hydrochloride, TBTU and N-ethyldiisopropylamine in dimethyl-formamide.

Yield: 96 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 19:1)

$C_{34}H_{23}F_3N_2O_2$ (548.57)

Mass spectrum : $(M-H)^-$ = 547

$(M+H)^+$ = 549

$(M+Na)^+$ = 571

Example 128

N-(2-aminocarbonylethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, beta-alaninamide, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 61 % of theory

R_f value: 0.53 (silica gel; dichloromethane/ethanol = 19:1)

$C_{24}H_{20}F_3N_3O_3$ (455.44)

Mass spectrum : $(M-H)^-$ = 454

$(M+H)^+$ = 456

Example 129

N-(1-aminocarbonyl-2-phenyl-ethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, D,L-phenylalaninamide, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 73 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{30}H_{24}F_3N_3O_3$ (531.53)

Mass spectrum : $(M-H)^-$ = 530

$(M+H)^+$ = 532

Example 130

N-[4-(1,4-Dioxa-spiro[4.5]dec-8-yl)-phenyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 4-(1,4-dioxa-spiro[4.5]dec-8-yl)-phenylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 90 % of theory

R_f value: 0.77 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{31}F_3N_2O_4$ (600.64)

Mass spectrum : $(M-H)^-$ = 599

$(M+H)^+$ = 601

$(M+Na)^+$ = 623

Example 131

N-(1-phenylmethylaminocarbonyl-ethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 2-amino-N-benzyl-propionamide, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 73 % of theory

R_f value: 0.74 (silica gel; petroleum ether/ethyl acetate = 3:2)

$C_{31}H_{26}F_3N_3O_3$ (545.56)

Mass spectrum : $(M-H)^-$ = 544

Example 132

N-(aminocarbonylmethylaminocarbonylmethyl)-3-(4'-trifluoro-methylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, H-Gly-Gly-NH_2 (glycylglycinamide), TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 71 % of theory

R_f value: 0.75 (silica gel; petroleum ether/ethyl acetate = 3:2)

$C_{25}H_{21}F_3N_4O_4$ (498.46)

Mass spectrum : $(M-H)^-$ = 497

$(M+H)^+$ = 499

Example 133

N-(1,2,3,4-tetrahydronaphthalin-1-yl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 1,2,3,4-tetrahydro-naphthalin-1-ylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 72 % of theory

R_f value: 0.60 (silica gel; dichloromethane/ethanol = 19:1)

$C_{31}H_{25}F_3N_2O_2$ (514.55)

Mass spectrum : $(M-H)^-$ = 513

$(M+H)^+$ = 515

Example 134

N-(4-tert.butoxycarbonylaminomethyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 4-(tert.butoxycarbonyl-aminomethyl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 89 % of theory

R_f value: 0.70 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{32}F_3N_3O_4$ (603.64)

Mass spectrum : $(M-H)^-$ = 602

$(M+Na)^+$ = 626

Example 135

N-(3-tert.-butoxycarbonylamino-propyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 3-tert.-butoxycarbonyl-amino-propylamine, TBTU and N-ethyldiisopropyl-amine in dimethylformamide.

Yield: 71 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 19:1)

$C_{29}H_{30}F_3N_3O_4$ (541.57)

Mass spectrum : $(M-H)^-$ = 540

$(M+H)^+$ = 542

Example 136

N-(3-dimethylamino-propyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, N,N-dimethyl-1,3-propane-diamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 26 % of theory

R_f value: 0.08 (silica gel; dichloromethane/ethanol = 9:1)

$C_{26}H_{26}F_3N_3O_2$ (469.51)

Mass spectrum : $(M-H)^-$ = 468

$(M+H)^+$ = 470

Example 137

N-[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 4-(1,2,3,4-tetrahydroisoquinolin-2-yl)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 20 % of theory

R_f value: 0.30 (silica gel; dichloromethane/ethanol = 50:1)

$C_{37}H_{30}F_3N_3O_2$ (605.66)

Mass spectrum : $(M-H)^-$ 604

$(M+HCOO)^-$ 650

$(M+H)^+$ = 606

Example 138

N-[3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl-carbonyl)-phenyl]-4'-trifluoromethylbiphenyl-2-carboxylic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 8 % of theory

R_f value: 0.50 (silica gel; dichloromethane/ethanol = 19:1)

$C_{32}H_{27}F_3N_2O_4$ (560.57)

Mass spectrum : $(M-H)^-$ = 559

$(M+H)^+$ = 561

$(M+Na)^+$ = 583

Example 139

N-{3-[5-dimethylaminomethylcarbonylamino-1,3-dihydro-isoindole-2-carbonyl]-phenyl}-4'-trifluoromethylbiphenyl-2-carboxylic acid amide

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, N-(2,3-dihydro-1H-isoindol-5-yl)-2-dimethylamino-acetamide, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 87 % of theory

R_f value: 0.70 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{29}F_3N_4O_3$ (586.62)

Mass spectrum : $(M-H)^-$ = 585

$(M+H)^+$ = 587

Example 140

N-[Cyclopropyl-(4-methoxy-phenyl)-methyl]-3-(4'-trifluoro-methyl-biphenyl-2-carbonylamino)-benzoic acid amide and N-[1-(4-methoxy-phenyl)-butyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide in the ratio 1:1

Prepared analogously to Example 34 from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, a 1:1 mixture of 1-(4-methoxy-phenyl)-n-butylamine and C-cyclopropyl-C-(4-methoxy-phenyl)-methylamine in the ratio 1:1, TBTU and N-ethyldiisopropylamine in dimethylformamide.

Yield: 18 % of theory

R_f value: 0.80 (silica gel; petroleum ether/ethyl acetate = 3:2)

N-[Cyclopropyl-(4-methoxy-phenyl)-methyl]-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

$C_{32}H_{27}F_3N_2O_3$ (544.58)

Mass spectrum : $(M+H)^+$ = 545

N-[1-(4-methoxy-phenyl)-butyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

$C_{32}H_{29}F_3N_2O_3$ (546.59)

Mass spectrum : $(M+H)^+$ = 547

Example 141

N-[1-(4-bromophenyl)ethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 1-(4-bromophenyl)ethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{28}H_{23}BrN_2O_2$ (499.41)

Mass spectrum : $(M-H)^-$ = 497/499 (bromine isotopes)

Example 142

N-[1-(4-Chloro-phenyl)ethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 1-(4-chlorophenyl)ethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{28}H_{23}ClN_2O_2$ (454.96)

Mass spectrum : $(M-H)^-$ = 453

Example 143

N-[1-(2-naphtyl)ethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 1-(2-naphtyl)ethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{32}H_{26}N_2O_2$ (470.57)

Mass spectrum : $(M+ Na)^+$ = 469

Example 144

N-{2-[4-(4-hydroxyphenyl)phenyl]ethyl}-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 2-(4'-hydroxybiphenyl-4-yl)ethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{34}H_{28}N_2O_3$ (512.61)

Mass spectrum : $(M-H)^-$ = 511

Example 145

N-[2-(4-benzyloxyphenyl)ethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 2-(4-benzyloxyphenyl)ethylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{35}H_{30}N_2O_3$ (526.63)

Mass spectrum : $(M+H)^+$ = 527

Example 146

N-(Benzo[1,3]dioxol-5-ylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 3,4-(methylenedioxy)-benzylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

$C_{28}H_{22}N_2O_4$ (450.49)

Mass spectrum : $(M-H)^-$ = 449

The following compounds may be prepared analogously and by methods known from the literature:

(1) N-(3,4-dimethoxy-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(2) N-[3-(4-biphenylyl)-prop-2-enyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(3) N-(4-aminomethyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(4) N-[4-(1,4-dioxa-spiro[4,5]dec-8-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(5) N-[4-(1,4-dioxa-8-aza-spiro[4,5]dec-8-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(6) N-[4-(4-oxocyclohexyl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(7) N-[4-(5-dimethylaminopyridin-2-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(8) N-(2-dimethylaminoethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(9) N-[3-(4-biphenylyl)-prop-2-ynyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(10) N-[3-(4-tert.butylphenyl)-prop-2-ynyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(11) N-[3-(4-tert.butylphenyl)-propyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

(12) N-[3-(4-biphenylyl)-propyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Example 147

Tablets containing 5 mg of active substance per tablet

Composition:

active substance	5.0 mg
lactose monohydrate	70.8 mg
microcrystalline cellulose	40.0 mg
sodium carboxymethylcellulose, insolubly crosslinked	3.0 mg
magnesium stearate	1.2 mg

Preparation:

The active substance is mixed for 15 minutes with lactose monohydrate, microcrystalline cellulose and sodium carboxymethylcellulose in a suitable diffusion mixer. Magnesium stearate is added and mixed with the other substances for another 3 minutes.
The finished mixture is compressed in a tablet press to form facetted flat round tablets.
Diameter of the tablet: 7 mm
Weight of the tablet: 20 mg

Example 148

Capsules containing 50 mg of active substance per capsule

Composition:

active substance	50.0 mg

lactose monohydrate	130.0 mg
corn starch	65.0 mg
highly dispersed silicon dioxide	2.5 mg
magnesium stearate	2.5 mg

Preparation:

A starch paste is prepared by allowing some of the corn starch to swell in a suitable amount of hot water. The paste is then left to cool to room temperature. The active substance is premixed for 15 minutes in a suitable mixer with lactose monohydrate and corn starch. The starch paste is added and the mixture is mixed with sufficient water to produce a moist homogeneous mass. The moist mass is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Highly dispersed silica is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is packed into empty size 1 hard gelatine capsule shells using a capsule filling machine.

Example 149

Tablets containing 200 mg of active substance per tablet

Composition:

active substance	200.0 mg
lactose-monohydrate	167.0 mg
microcrystalline cellulose	80.0 mg

hydroxypropyl-methylcellulose, type 2910	10.0 mg
poly-1-vinyl-2-pyrrolidone, insolubly crosslinked	20.0 mg
magnesium stearate	3.0 mg

Preparation:

HPMC is dispersed in hot water. After cooling, the mixture yields a clear solution.

The active substance is premixed in a suitable mixer for 5 minutes with lactose monohydrate and microcrystalline cellulose. The HPMC solution is added and the mixing is continued until a homogeneous moist composition is obtained. The moist composition is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Poly-1-vinyl-2-pyrrolidone is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is compressed in a tablet press to form oblong tablets (16.2 x 7.9 mm).

Weight of a tablet: 480 mg